

The cell cycle related rhythms, cells' states correlation and the cancer

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We consider the decision making by mammalian cells, looking them as dynamic systems with rhythms. We calculate the effective dimension of the cell division model of the healthy mammalian cells consistent with the data: it is described via a four dimensional dynamic system. We assume that the cell's decision making property is strongly affected by the cells rhythms, their causal relations, and by the correlation between internal states of different cells in tissue. There is a strong correlation between the states of different healthy cells (verified partially experimentally), and we assume that there is no such a correlation between internal states of the healthy and cancer cells. The origins of the cancer are just the disruption of this correlation (self-identification of the cells) and the change of the causal relations between the Circadian and cell cycle rhythms. Assuming the Gaussian channel version of the cell-cell communications and a key role of public goods for the cancer cells, we get a strong correlation between the states of different cancer cells.

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I. INTRODUCTION

Among the key features of cancer the wrong division process of the cells [1] and evolutionary dynamics aspects of the cell proliferation [2] are well known. In the recent paper [3], it has discussed cancer as a breaking of cooperation in multicellularity, and looked at 5 aspects: cheating in proliferation inhibition, cell death, division of labor, resource allocation, and extracellular environment maintenance. Why does the normal multi-cellularity fail? According to [4-7] the (bacterial) cell has an internal representation of the environment. It is connected somehow with the dynamics of regulatory networks. It is possible to estimate even the information capacity of the cells, and in the case of bacteria, it has been estimated as a few bits [8]. In [9] we found different phases in the dynamics of the reaction networks and related the origin of the cancer with the change of the dynamic phases of reaction networks. In recent experimental work [10], the statistics of the healthy mammalian cell division times have been analyzed by measuring the L1210 lymphoblasts division periods for different off springs of the same cell. They fitted the data by a deterministic model and concluded that the healthy cell's division dynamics have an effective dimension of three.

In L. Schwartz et al, "Cell proliferation as the consequence of a balance between Pentose Phosphate Pathway and Mitochondrial Metabolism," several oscillations (ATP, NADH/NAD⁺, Ph concentrations) have been found in the case of the healthy colon cells, while absent in the cancer case. We interpret these oscillations as related with the internal state of the cell and sensing abilities of the cells allowing proper multi-cell decision making, and explain the cancer as a lack of the mentioned abilities. In [11] the common sensing of the concentration gradients has been investigated, and it has been concluded that a strong correlation exists between cells related to each other by 3-4 neighbor contacts. In [11] the authors considered the case of the relay channel [12] for information processing of n cells located on a 1-d chain, and its environment. Fig. 1.a describes the case $n = 2$. Cell A senses the environment and sends a signal to the cell B, which also gets a signal from the environment as well. In [13], the correlation of the calcium fluctuations in different mammalian cells on 2-d surface have been investigated including some fraction of cancer cells. We will correct the mathematical result of [10], then give our interpretation of the results [11],[13].

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II. THE CELL AS FOUR DIMENSIONAL DYNAMIC SYSTEM DURING THE DIVISION PROCESS

In ([10] the following system of iterative equations has been suggested to define T_n , the duration of the cell division period after n divisions:

$$\begin{aligned}
 T_{n+1} &= T_0(1 - \alpha) + T_n + \sin(2\pi t_{n+1}) + \epsilon^\pm \\
 t_{n+1} &= T_n + t_n \\
 \epsilon^\pm &= \beta(X_{n+1}^\pm - Y_{n+1}^\pm) \\
 X_{n+1}^\pm &= 2(X_n \pm \delta) + (Y_n \pm \delta) \text{Mod}(1) \\
 y_{n+1}^\pm &= (X_n \pm \delta) + (Y_n \pm \delta) \text{Mod}(1)
 \end{aligned} \tag{1}$$

Here T_n, t_n, X_n, Y_n are dynamical variables, and this is 4-dimensional dynamic system. t_n is the absolute time, X_n, Y_n are introduced to describe the fluctuations of the cell division period T_n while $\alpha, \beta, \delta, T_0$ are the parameters of the model. The model fits experimental data well for the correlation of division periods for different offsprings of the same cell. It describes a map kicked by the oscillator, plus a small term, derived using a highly chaotic cat map for X_n, Y_n .

We can remove t_n , then in the argument of \sin we will get a sum $T_n + ..T_1$, which is a strongly non-Markovian behavior. In [10] the Grassberger-Procaccia algorithm has been used to calculate the effective dimension of a dynamic system. One puts the points $(T_n, T_{n+1}, \dots, T_{n+d})$ into d -dimensional "embedding" space, then fits the number of these points in a d -dimensional sphere $N(r)$ as some degree of r (the distance from some reference point), such that $N(r) = cr^{n(d)}$. Then $n(d)$ is just the correlation dimension. $n(d)$ grows with d , and for finite dimensional dynamic systems goes to a plateau at high values of d . We denoted by D the limiting value of $n(d)$. D is the effective dimension of dynamical system, characterizing its attractor dimension. The behavior of $n(d)$, does not carry any information about the dynamical system, only the plateau value D is important. We have done numerics for 10^8 points, fitting the correlation dimension at the middle scales. We took the following values for the parameters: $T_0 = 0.75, \alpha = 0.5, k = 0.1, \delta = 0.15, \beta = 0.12$, measuring the time in days [10]. Then we get the results given by n_2 in Table I while the results of [10] are denoted by n_1 . Our results support the value $D = 4$. The correct value of effective dimension is important for the applications. Thus, according to experimental results of [10], the cell could be considered as a deterministic 4 dimensional system. In [10] a wrong result, $D = 3$, has been derived as a consequence of the short number of iterations and of the measuring the distribution at a small distance. We replaced the cat map by tent, Hennon or logistic maps and obtained that the effective dimension is around 2. Therefore, these maps cannot describe the data of [10]. The choice of the correct model, done in [10], is a really genuine finding.

TABLE I: The correlation dimensions n_1 from [10] and our numerical result n_2 versus the embedding dimension d . The maximal value of n_2 is close to 4, an effective dimension of the system.

d	2	3	4
n_1	1.65	2.05	2.1
n_2	1.91	2.99	3.93

III. THE DECISION MAKING BY THE CELLS

A. The decision making scheme

During its lifetime a cell changes the phase of mitosis, cooperates with other cells and reacts to the extracellular stimuli. All of these processes are predefined by the genetic code. However, the cells do not simply follow instructions, but they are able to make decisions based on the received information [14]. We can concretize the decision making scheme by looking at the states (internal images), sensing, and action [14]. Additionally, we identify the cell states with the attractor points of the dynamics of the reaction networks or gene regulation networks. The transitions between the attractors correspond to the change of phenotypes [15], and tradeoffs. The cells can construct their internal representations of the environment by using the memory of the regularity networks, similar to the case of neural networks [4].

In Table II we suggested a hierarchical scheme while looking at different aspects of decision making. There are more deterministic, physical factors, like metabolism, polarization, pressure and stiffness, as well as more probabilistic factors related to information processing. We assume as a hypothesis (**Hypothesis I**) that the decision making by the cells is defined by some key rhythms, their correlation and casual relations. The causal relation between Circadian and cell-cycle rhythms has been investigated in [16] for the concrete version of mammalian cells. According to [17], the choice of pacemaker (circadian rhythm or cell-cycle) depends on the concrete case of the cell.

TABLE II: The cell state with different level of coarse-graining and decision making.

Level	
Decision making	
4	Collective rhythms, their causal relations
3	The environment's images, regulation networks' states, information processing
2	Metabolism, polarization, pressure
1	Un-equilibrium statistical mechanics.

B. The rhythm as a compressed description of the complex system

In living systems, we see a specific form of non-equilibrium statistical mechanics (metabolism) and information processing [18]. Then we add to this scheme the collective rhythms, their correlations and causal relations. Our suggestion assumes a more reliable scheme of decision making than the direct influence of metabolism and information processing. The phases of the rhythms in living system, and the correlations between rhythms give examples of compressed information. Gell-Mann and Lloyd [19] defined compressed information as a key feature of the complex adaptive system, see also [20]. The synchronization of different rhythms is an important characteristic of health which is well known in biomedicine data analysis [21,22]. We put the decision making property at the top of the hierarchy (see [20] for the hierarchy of "reflections" in complex systems) levels, higher than the information processing.

The rhythms give a simple description of the dynamics, everything is almost the same besides the single variable "phase" which is not changed. In quantum mechanics, the state of the system simply rotates in the Hilbert space while during the measurement there is an irreversible event, a collapse of wave function. The irreversible event of cell division is equivalent to the collapse of the wave function. In quantum mechanics, there is also a property like decision making due to dual property: the same object is both a particle and a wave. The causal relations between rhythms resembles a dual aspect of quantum-mechanical systems. We need at least two "independent" oscillations to have this quantum mechanical analogy and decision making, like in mutation-selection pair in evolution models, to get a quantum-mechanical mathematical structure in evolutionary dynamics [20].

IV. THE CORRELATION BETWEEN THE INTERNAL STATES OF THE CELLS

A. The correlation

Let us first define the state of the cell more accurately, see Table III. The concept of the state includes both the steady state of gene regulation network GRN, and the dynamic memory related to the GRN bi-stabilities as has been discussed for the case of bacteria [4,5,6]. To understand the multi-cellular phenomenon, we should look at the sensing environment (chemosensing, mechanosensing, photosensing), as well as the cell-cell interactions (communications). The mammalian cells can sense collectively much stronger than separately [23]. Due to fast information transition between neighboring cells, they are undergoing a "coherent" signal detection by several cells, suppressing the noise-signal ratio. Actually, the fast communication amongst the cells allows collective information processing for $n = 3 - 4$ layers of cells, suppressing noise-signal ratio threshold n^2 times [11]. In [13] the correlation of Ca concentration's fluctuations in the ensemble of mammalian cells (mouse fibroblast NIH 3T3 cells) has been analyzed including some fraction of the cancer cells (MDA-MB-231).

We assume **Hypothesis II**: there is a correlation between internal states of different healthy mammalian cells in tissue, rhythms, and fluctuations. The correlation of internal images of the cells allows common information processing and therefore also common decision making by a collection of the cells. Without the former, the latter certainly could not work efficiently.

For the diffusive molecule, it should be easier to go from one molecule to a neighboring one when they oscillate coherently, as it is easier to jump from one moving car to another one, moving in parallel. The correlation between the states of the cells can be organized both by pressure and communication between the cells. In [13], the cell-cell communication (diffusion) rate via a gap junction has been found to be much weaker in the cancer case, typically 30%-40% of the healthy cells, and the response dynamics is slow. If we assume a correlation between internal states, it is reasonable to look for the fluctuations of different

TABLE III: The state of the cells.

Level	
3	The phases of the rhythms
2	Internal images of the environment.
1	The dynamic memory of gene regulation network
0	The steady state of gene regulation network

cells. According to [24], the correlation of the Calcium fluctuations in different mammalian cells decreases rather slowly with the distance d between the cells, like $\sim 1/d^b$, $b \approx 0.2$, which supports our hypothesis. Some large scale synchronization has been observed in the fluctuations of Ca concentration in [13]. The common sensing of 3-4 cell layers, the correlation between the fluctuations of the Ca-es concentrations, and the correlation of Circadian clocks of thousands cells [25] are three particular cases of the correlation between the cells' states in the tissue. We claim that the correlation is a rather general phenomenon.

B. The multi-terminal model

We formulated our hypothesis II about correlation between internal states of the cells. Now we will formulate a mathematical model for information processing by the collection of the cells. Different cells sense the environment and can also communicate with each other, see Fig. 1b. We can replace such a multi-terminal system by another one, where the cells just sense the environment. In this case, however, there is a correlation between the states of different cells. We considered such a model in [26]. Identifying the information transmission capacity of both systems, we define the degree of correlation between the states of different cells.

We can qualitatively describe the situation as a decoding of information via two decoders, related by an almost errorless discrete information channel. Later, we will look at the realistic case of the Gaussian channel. We consider a two letter alphabet. Let us assume that cell A gets the encoded signal, z letters ± 1 , where the probability of the error is $1 - p_1$, and original message about the environment signal has N bits. In the same way, the second cell B receives a signal of z bits under the noise probability $1 - p_1$. If there is no communication between the cells, the correct decoding is possible when [12]

$$N \ln 2 \leq z(\ln 2 - h(p_1)) \quad (2)$$

where $h(p) = -p \ln p - (1 - p) \ln(1 - p)$ defines the information content of one letter of the noisy signal as $\ln 2 - h(p_1)$, while original message has $N \ln 2$ bit information.

We model the collection of the cells as a multi-terminal system according to Fig. 1.b. Thus, in our system, there is an information transmission in both directions. Let us assume that there are communications between the two cells with an error probability $1 - p$ and cell A sends to cell B just its signal from the environment. A simple consideration gives the following condition for the errorless decoding:

$$N \ln 2 \leq z[(\ln 2 - h(p_1)) + (\ln 2 - h(p_2))] \quad (3)$$

where $p_2 = p_1 p + (1 - p_1)(1 - p)$. Thus, our system has a better information processing ability than single cells and can decode correctly weaker signals with a smaller z/N .

When $p \rightarrow 1$, our system has the same decoding performance as the model with strongly correlated (identical) states [26]

$$N \ln 2 \leq 2z[\ln 2 - h(p_1)] \quad (4)$$

If we remove the correlation between the terminals ($p \rightarrow 1/2$), the correct decoding of information, and, therefore, the decision making is impossible [26]. The loss of correlation between the states of the cells can play a dramatic role, as information processing in the cell is near the threshold of correct decoding of noisy information [27].

According to the experimental results of [28,13], cell-cell communication is weaker between the cancer cells, the same as with the correlation of the internal states. Therefore, according to our interpretation of the cells ensemble (as a multi-terminal system), for the cancer case, the multi-terminal system is below the threshold to construct a normal tissue.

Let us consider another model, when the states of two cells are correlated, there are $2^{N(2-C)}$ configurations, less than all the possible ones 2^{2N} . Thus, C defines the correlation level, and $C = 1$ is the perfect correlation. These cells sense the environment.

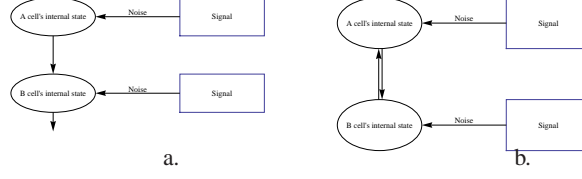


FIG. 1: Looking the collection of the cells as a multi-terminal system. The system is decoding the noisy information to make a decision. (a). The relay channel from [11]. Both cells sense the signal from the environment. Cell A sends a signal to the cell B, which also sense the environment, and gives as output the decoded information. (b) There is a fast information transition between two cells, which also senses the environment.

We get for the error threshold of the model:

$$N \ln 2(2 - C) \leq z[\ln 2 - h(p_1) + \ln 2 - h(p_1)] \quad (5)$$

Let us identify the error threshold of our model with the error threshold given by eq. 3. Then we obtain the effective value of the correlation C .

A strong correlation means $(1 - C) \ll 1$. We see that in order to get a strong correlation between healthy and cancer cells, we need a communication with minimum errors. In the case of errorless cell-cell communication ($p = 1$), there is a complete correlation between the states of two cells.

We can write the solution of the system of eqs. 3,5 as

$$C = \frac{I_{cc}}{I_t} \quad (6)$$

where I_{cc} is the information transmission rate between cells (related to the environment state), and I_t is the total information transmission rate between the cell, other cells and the environment (related to the environment state). In case of Gaussian channel, eq. 6 is equivalent to the constraint that the signal noise ratio for the communication between neighboring cells is much stronger than for the sensing of the environment.

While looking at the correlation between the states of different cells, we should also look at images of different environmental factors. When we put the cancer cells in a new environment [13], they act as normal cells. We can understand the situation in our scheme, using eq. 6. The information exchange between the cancer cells and healthy cells is the main fraction in total information transmission of the cancer cell; therefore, the internal state of the cancer cell is still correlated with the states of healthy cells.

C. The synchronization and correlation of the states of cancer cells

We claim that for collective decision making, the ensemble of the cells should have correlated internal states. For the cancer cells, the correlation is not enough to organize a healthy tissue. Nevertheless, it can be enough for some correlation for a large enough ensemble of the cells. One possibility for communication among the cancer cells is through the diffusive molecules by an all-to-all scheme. Let us regard the cells as just oscillators with randomly distributed frequencies. Thus, we are characterizing the internal state of the cell just via a phase. There is a simple interaction between the oscillators, decreasing with distance. Consider the Kuramoto model where N oscillators are defined in the space [29]

$$\frac{d\phi}{dt} = \omega_i + \frac{K}{\eta} \sum_j \frac{1}{r_{ij}^\alpha} \sin(\phi_j - \phi_i), \quad (7)$$

where ω_i are the internal frequencies of the cells and have some random distribution, η is a normalization constant, and r_{ij} is the distance between the oscillators. For $\alpha \leq 1$, a complete synchronization has been found for the sufficient large population of the cells. The threshold value of the population is defined by α and K . Thus, there is a minimal population size for synchronization. We can qualitatively understand the growth of the tumor, assuming a minimal size necessary for synchronization, and therefore, for collective decision making by a tumor. We claim that a large distance correlation between the cells' internal states is possible (see also [13]). Even if the cancer cells communicate weakly with each other, they can sense the environment signals, and, according to eq. 6, they can get strong correlation between internal images.

Let us derive a similar result using a multi-terminal model approach. Different cells sense the environment and communicate with each other via diffusive molecules, typical for the case of public goods [30] using the Gaussian information channel [11,12]. Now the error threshold is given by

$$N \ln 2 \leq z \sum_j \frac{(J_i)^2}{2j^2}, \quad (8)$$

where J_i is the strength of the signal from the i -th cell to the given one, while j is the noise intensity. We assume that due to diffusion $J_i \sim 1/r_i$, where r_i is the distance to the i -th cell, and there is a uniform distribution of the cells in the space. The right hand side of eq. 8 grows linearly with the maximal distance L , and we get from eq. 8

$$(1 - C) \sim 1/L, \quad (9)$$

where L is the tumor size (diameter). Thus, the cells' states are strongly correlated, as in the case of Kuramoto model.

Our result, eq. 9, supports strong cooperation of the cancer cells. Therefore, while independent replicator models of cancer are useful at the first stage of disease [31], we have to take into account the cell-cell interaction later. According to [7], a cooperation between the regularity networks of different cells in tissue can drastically increase the associative learning ability of cancer cells, $\sim N$ instead of $\sim \sqrt{N}$ [7] where N is the number of bi-stabilities. The associative learning should be considered as the main arsenal of adaptability of cancer cells: short evolution periods in the case of cancer does not allow more involved schemes of adaptability. We interpret the results of [6] that the cell-cell cooperation can increase the adaptability potential by about 10 times. We assume that this drastic increase in adaptability is possible only because of the strong correlation of the cells' states.

In [13], it has been assumed that the cell ensemble works near the critical point (via cell-cell communication parameters) which allows a control of the cell dynamics via a cell-cell communication level. We assume that for a proper cooperation of cancer cells, it is necessary and sufficient to have strong enough cell-cell communication and metabolism efficiency (to support the former). Then after further degradation of these features, they will fail to cooperate. In principle, the cancer cells can organize a correlation between their internal states using both diffusive molecules and gap junctions [32], as the latter have about 60-70 % of the communication rate of a healthy cell. It is very important to identify which communication scheme plays a key role, especially in case of metastasis. Perhaps in this way, we can understand the metastasis as a new phase where a large scale cooperation of cancer cells stop to work.

V. CONCLUSION

In conclusion, we derived rigorous mathematical results (four as an effective dimension of healthy cell division dynamics; a strong correlation of internal states of the cancer cells in the tumor) as well as suggested several hypothesis to understand the cell decision making and cancer which can be verified experimentally. If we look to the cancer as a complex dynamical (statistical physics) phenomenon, then the first step should be the identification of the effective dimension of the phenomenon; otherwise, a serious investigation of the system is impossible. We are trying to give a maximally compressed, but still reasonable understanding of the considered complex phenomena and suggest the comparative analysis of healthy and cancer cells by looking at the cell effective dimension during the division, the existence of energetic cell-cycle related rhythms, the correlation between internal states of the cells in tissue, the fractions of gap junction, and diffusive molecules in the cell-cell communications. We assumed a hypothesis that the rhythms of the cell (circadian and cell-cycle) strongly affect the decision making process. Instead of relating the origin of the cancer with the change of one rhythm (i.e. a disruption of circadian rhythm; see a critical review in [17]), we suggest to look at the rhythm-rhythm interaction. We also considered a simple model and derived the expression for the correlation of the internal images of different cells. Our claim is that an efficient collective decision making by the cells is possible only by having a strong correlation of internal images. The cancer cells have less effective information processing ability and that's why they can not support a normal homeostasis. Nevertheless, there is some correlation between the cancer cells' states. Assuming just a gaussian property for the cell-cell information channel and public goods as the main mechanism of interaction of cancer cells, we derived our key result eq. 9 : a strong correlation of the states of the cancer cells. Actually, strong correlation of internal states can bring self-identification of a group of the cells. We used a simple model. We need also to look at how the cell-cell communication errors affect a strong increase of dynamic memory for associative learning by the ensemble of the cells as found in [6]. We need to clarify which version of cell-cell communication (via diffusive molecules or gap junction) is more important in the case of cancer and metastasis. The metastasis phase can be related with the transition from long-ranged correlation among the cancer cells to short range correlation.

As the rhythms and correlation of internal states of the cells are crucial in our approach to cancer, we suggest that the experiments [10,16] are repeated for the cancer case, followed by ATP rhythm looking for the metastasis, and for the tumor after metabolic treatment [33], looking for the rhythms and their correlations. Especially interesting would be to repeat [13] for the metastasis case, measuring the cell-cell correlation for calcium in case of the cancer-metastasis cell and metastasis-metastasis cases. Before applying the treatment strategy against the public goods, related to the diffusive molecules [30], we should clarify

which version of communication plays a key role in case of cancer and metastasis. We should investigate the causal relation between different rhythms in other living systems [22], as well as construct a simple models for the system with several rhythms and decision making. We assume that the cancer's treatment should be looked at from the both physical aspects (correcting the metabolism [33], the acidity [34]) and decision making aspects (acting on the rhythms interaction).

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